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TRANSMISIÓN SINÁPTICA SYNAPTIC TRANSMISSION

Presidente (Chairman): I. BROWN

ANICHKOV, S. V., Pharmacology of the central cholinergic synapses. — (*Pharmacological Department, Institute of Experimental Medicine, Leningrad, USSR.*)

The admission of the role played by acetylcholine as one of the mediators in central intraneuronal synapses has led to the idea that there must exist in these synapses, some sort of cholinergic structures responding to certain cholinomimetic and cholinolytic drugs. In the physiological analysis of central cholinergic mediation, extensive use has been made of such pharmacological agents, as acetylcholine, nicotine, physostigmine, and atropine, applied mostly locally. Data concerning the nature and location of central cholinergic synapses have appeared in the well-known researches of Feldberg, Marrazzi, Bovet and Longo, in the lectures delivered by Minz, and in several reviews of the subject.

The aim of the present paper is to approach this problem from a purely pharmacological viewpoint, namely to dwell on the role played by the central synapses in the resorptive action of the agents affecting cholinergic transmission.

Unfortunately, up to now there have been but few pharmacological investigations into the central action of resorbed cholinomimetic agents, though some of them are widely used in everyday life. Suffice it to mention the central action of nicotine upon smokers, or arecoline upon betel chewers. Though the central action in these stuffs is considerable and peculiar in character, research work has been mainly concerned with their peripheral action.

There is, it is true, a number of researches (Zhuravlyov, 1938; Novikova, 1940) showing that even small doses of nicotine first stimulate and then disturb conditioned reflexes. The same effect has been ascertained in arecoline (Denissenko, 1958). It is worth-noting that a change from tertiary to quaternary bonds in the nitrogen atom both of nicotine and areco-

line abolishes their action upon the CNS (Lukomskaya, 1957). But there is as yet no work upon the central action of cholinomimetics that might lead to the therapeutic use of any of them.

Almost as little is known about the pharmacology of the central influence of anticholinesterases. They exert undoubtedly a powerful action on the CNS depending mainly upon the stabilization of mediator acetylcholine in central synapses. In certain anticholinesterases, fluororganic compounds, for instance, central action, if we infer it from symptoms of poisoning, largely predominates. Central acting cholinesterases are successfully applied in treating certain forms of central paralysis. Still, there exist very few experimental researches upon the subject.

Relatively more is known about the central action of cholinolytic drugs, and here Soviet pharmacologists have obtained some new data. Accordingly, the present paper, which embodies a review of Soviet work in this field, will be mostly concerned with this aspect of the pharmacology of central cholinergic synapses.

During the last few years quite a number of cholinolytic drugs have been synthesized and experimented with. They have been described as atropine-like substances. Some of them possess properties differing from those of atropine proper. There is, in particular, a certain group of drugs which have a stronger action upon the central synapses than upon the peripheral ones. From the viewpoint of dependence of action upon structure most interesting are the drugs structurally related to acetylcholine. Their cholinolytic action may be interpreted as competitive antagonism between two substances nearly related in structure. We know that by giving more bulk to the acid part of the acetylcholine molecule we may obtain its antagonist. But cholinolytics of this kind, while possessing a strong peripheral action, have little or no effect upon the cholinergic synapses of the brain.

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Most probably, this small central effect stands in some relation to the fact that compounds of this kind, being quaternary ammonium salts, carry an electric charge, and are but slightly soluble in lipoids. Indeed, when we pass from similar compounds to corresponding tertiary amines, we find stuffs possessing a lesser peripheral and a stronger central cholinergic action. The following chemical properties are common to stuffs of this description: most of them are esters of diethylaminoethanol or nearly related alcohols and aromatic acids. Among such compounds the one possessing the simplest structure is the ester of diphenylacetic acid and diethylaminobenzene, known under the names of trasentin, diphenal and spasmolytic.

This drug was the starting point of our investigations. There was a time when trasentin was considered only as a substitute for atropine in its peripheral action, though in this respect it is far less active. But its action upon the cholinergic synapses of the cerebrum compared with its peripheral action, is relatively strong. Predominant action upon the CNS is also encountered in nearly related esters and thioesters. Certain cholinolytics introduced as drugs for treating parkinsonism (paraparic and others), have also a preponderant action upon the central cholinergic synapses. All similar substances may be called central cholinolytics.

The preparations of this group mainly used by Soviet pharmacologists and clinicians are the following:

1. Trasentin (diphenal); ester of diphenylacetic acid and diethylaminobenzene;
 2. Aperitol; ester of o-phenylacetic acid and diethylaminobenzene;
 3. Aperidol; ester of diphenylpropionic acid and diethylaminobenzene;
 4. Dimetyl; ester of diphenylglycolic acid and diethylaminoethanol;
 5. Ganglion; ester of para-substituted benzoic acid and γ -diethylamino- α , β -dimethylpropenol;
 6. Thiphene; ester of thiobisphenylacetic acid and diethylaminoethanol;
- Two other small group may be included drugs possessing cholinolytic properties, but having entirely different structures, as for example simple esters and amides, but I shall not dwell upon them, as it would unduly complicate the issue.

The preponderant action of the central cholinolytics upon the cerebrum is first perceived in the subjective sensations of the patient after the administration of therapeutic doses of the drug. Subcutaneous injection of trasentin to an adult in doses of 0.1-0.2 causes a sort of inebriation. Such doses, while producing dizziness, have as yet no typical peripheral cholinolytic effect, as, for example, dryness in the mouth or dilation of the pupils. This testifies to the preponderant central action of trasentin. The inhibitive effect of trasentin and other cholinolytics of the same group upon the CNS is corroborated by observations made upon the conditioned reflexes. Experiments upon dogs carried out according to the standard Pavlov method of conditioned salivatory reflexes have shown that trasentin injected subcutaneously in doses of 0.1 mg per kg impairs differential inhibition, that is, weakens the process of conditioned inhibition. Stronger doses of 1 mg per kilogram bring about a marked depression in both conditioned and unconditioned salivatory reflexes, in other words, they lead to a weakening of the excitatory processes in the cortex as well as in the subcortical areas (Krylow, 1955). These doses do not as yet produce any marked peripheral effect, in particular, they do not affect the innervation of the salivatory glands. The action of trasentin upon the unconditioned vegetative reflexes is also apparent in the secretion of the alimentary tract. Trasentin in doses of 5 mg per kg greatly depresses reflex gastric secretion during sham feeding and calomel-induced reflex hypersecretion of intestinal juices (Savitch's calomel test). This action is not wholly attributable to the peripheral atropine-like action of trasentin, as the same doses of the drug inhibit in a much lesser degree secretion caused by pilocarpine and eserine. Obviously, the more important part in this process is played by the action of trasentin upon the central link of the reflex arc (Melnikova, 1958). This conclusion is confirmed by the fact that inhibition of secretion caused by trasentin is abolished in its greater part by carbachol acting as is known upon the subcortical centres. The central action of trasentin and other central cholinolytics may be well perceived in electroencephalograms. When given to a rabbit, they cause a depression in the electric activities of the cerebrum and a change in the form of the

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oscillogram peculiar to cerebral inhibition.

The cholinolytic character of the central action of the stuffs belonging to this group is proved by the fact that they antagonize the central action of the cholinomimetics nicotine and arecoline.

The electroencephalographic changes seen in rabbits after nicotine and arecoline are abolished by trascentin and other central cholinolitics and vice versa (Longo, Berger and Bovet, 1954; Denissenko, 1958).

Accordingly, cholinolitics and cholinomimetics display in their effect upon the central cholinergic synapses not a one-sided but a double-sided antagonism. The same is seen in the case of conditioned reflexes (Lukoinskaya, 1957; Denissenko, 1958).

According to the well-known experiments of Bovet and Longo (1954), parapamite, trascentin and several other cholinolitics prevent central hyperkinesia provoked in rabbits by nicotine. Soviet pharmacologists (Golyakhovsky, 1949; Seinai, 1955; Kharaoosov, 1958; Golikov, 1956, and Sokolova, 1957) have shown that certain cholinolitics abolish arecoline-induced hyperkinesia. This phenomenon is best observed in mice. Another phenomenon convenient for the study of arecoline poisoning is the winking of pigeons (Kharaoosov, 1958). Under the action of arecoline it becomes markedly more frequent, and is soothed after introduction of some central cholinolitics.

Comparative studies have shown that while some central cholinolitics are particularly effective in antagonizing the central action of nicotine, others antagonize better the central action of arecoline (Seinai, 1955). Obviously, the difference observed in the peripheral effect of cholinolytic substances which are in part predominantly nicotinolytic and in part predominantly muscarinolytic, subsists in their central action, too.

Antagonism between central cholinolitics and nicotinic may manifest itself not only in the cerebrum, but also in the spinal cord:

It is a well-known fact that one of the early and striking symptoms of the central action of nicotine upon the frog is a peculiar cataleptic state with a very characteristic posture (so-called "worshipper posture"). As we have shown (Anitchkov and Grebyonkina, 1947), this state is brought about by nicotine acting upon the spinal cord. This action is cholinomimetic, as the same posture is observed when applying

acetylcholine to the spinal cord of the frog.

This nicotine-induced rigidity is relaxed and may be prevented by trascentin and other central cholinolitics. There also exists an antagonism between central cholinolitics and anticholinesterases (Mikhelson and assistants, 1954). Observations made on healthy subjects showed that psychic troubles induced by certain cholinesterases, as parpanite (3 mg per kg) did not appear, if 0.02 mg per kg of prostigmine was injected subcutaneously at the same time.

Mutual antagonism between cholinolitics and anticholinesterases was demonstrated upon the conditioned reflexes of animals, atropine, scopolamine, parpanite and several other synthetic drugs with predominantly central action (such as cholinolitics, and physostigmine and minatol (alias phosphacol, miotol) as anticholinesterases (Mikhelson and assistants, 1954; Rozhkova, 1957; Savateyev, 1957).

The Bulgarian pharmacologist Pavlov treated the subject of antagonism between central acting anticholinesterases and central cholinolitics, using trascentin and benactyzine, as cholinolitics, and the alkaloid nivalin alias galanthamine as anticholinesterase. This alkaloid was extracted by Soviet and Bulgarian pharmacologists from different species of snowdrop (*Galexia* *Vorontzovi*, *Galeatus* *krusius*).

Large doses of nivalin produce convulsions in animals. These, as well as the electroencephalic changes brought about by nivalin, are easily abolished by small doses of trascentin and benactyzine introduced into the subarachnoidal space. It follows that the action of the stuffs, which we have called cholinolitics, upon the CNS is actually cholinolytic and direct in character.

It is to be noted that though the action of cholinolitics upon the CNS is on the whole depressant, nonetheless, because of the complex interdependence of different areas, become, on the contrary, stimulatory. This is namely the case with the centers controlling ACTH secretion. Experiments carried out by Podol'shko at our laboratory (1957) have shown that trascentin and other central cholinolitics increase the cortical activity of the adrenals. This action was assayed on rats by estimating the ascorbic acid level in the adrenal and the number of eosinophils in the blood, and on dogs by direct evaluation of the amount of 17-

oxygenated corticosteroids secreted into the blood-stream.

Since central cholinolytics increase hormonal secretion of the adrenals only in animals with intact hypophysis, this phenomenon is evidently due to hypersecretion of ACTH.

The ganglion-blocking agent hexamethonium prevents this cholinolytic-induced hypersecretion just as it prevents reflex stimulation of ACTH secretion. This leads to the conclusion that central cholinolytics induce the excitation of the same hypothalamic centres which are stimulated by stress.

Some data concerning the interrelation of central action and structure in cholinolytics are available.

The addition of a hydroxyl radical to the acid residue at the carbon nearest to the carboxyl, that is, the transition to esters of the aromatic oxyacids, enhances the central cholinolytic action of the ester, the most pronounced action being upon conditioned reflexes. Thus, for instance, the ester of diphenylglycolic acid, benactyzine (alias, diazil) inhibits conditioned reflexes of dogs much more than unconditioned ones, while trasentin (an ester of the diphenylacetic acid) acts upon both with the same intensity (Krylov, 1955). Jacobson and Soraia (1958) have observed an increasing action of benactyzine on simple conditioned reflexes of rats and depressing action on more complex ones.

The character of the central action undergoes parallel changes. The esters of aromatic acids antagonize mostly the central action of acetylcholine, while the esters of acids devoid of hydroxyl have a predominant action upon the central influence of histamine (Kharkovskiy, 1955). The same is true when comparing the different properties of the esters of the same acids. Thus, the action of the esters of diphenylglycolic acid upon the cholinolytic structure of post-ganglionic synapses, or "muscarine-sensitive", or "muscimine-cholinoreactive systems", as we call them, that predominates in the latter, the preponderant action is upon the cholinoreactive structures of the ganglia, or, as we call them upon the "nicotine-sensitive" or "nicotinic-cholinoreactive systems".

Higher intensity of central action is observed in cholinolytics when oxygen is replaced by sulfur in the ester bond. Thus, the action of thiophene, which is a thioester,

is stronger than that of the corresponding ester trasentin.

The same relation exists between benactyzine and the corresponding ester.

It has been observed that the central cholinolytic action is strongest in some esters of the aromatic acids with an asymmetrical carbon atom in the alcohol or acid part of the molecule.

In all these cases, the intensification of the central action of cholinolytics goes hand in hand with the heightening of their peripheral effect.

Entirely different results are obtained by converting the tertiary amines into corresponding quaternary salts. Such a change in the structure of cholinolytics enhances the peripheral effect and causes a considerable lowering in the action upon the cortical and subcortical areas of the cerebrum, as has been shown by the work of the laboratory of Mikheilson (Mikheilson, Khromov, and others, 1954; Mikheilson and others, 1957). The same enhance of peripheral and lowering of central action takes place in anticholinestersases in cases of appearance of electric charge of the sulphur atom (Seimal, Mikheilson, Ribolovley, 1957).

The conversion of amines into quaternary ammonium compounds increases the toxicity of cholinolytics. Death from poisoning with quaternary nitrogen cholinolytics is brought about by stopping of respiration. The analysis of the cause of this phenomenon was carried out at our laboratory (Chaijkovskaya, 1958). For this purpose we used decerebrated cats and non-anesthetized rabbits and recorded simultaneously the electric activities of the diaphragmatic nerve and the diaphragm. It was found that after introduction of a lethal dose of alkyl halides of trasentin (methiodid and ethiodid) at the moment of breath stopping the electrical activity of the diaphragm disappears. It was shown that the initial cause of breath failure is a curare-like action of the quaternary salts. However, a few moments after the failure of the respiratory muscles there follows notwithstanding the application of artificial breathing, a stopping of the electrical activity of the diaphragmatic nerve, indicative of the irreversible paralysis of the respiratory centre.

It follows that the quaternary derivatives of trasentin, while acting but slightly upon the cerebrum, have a relatively strong inhibitory action upon the higher centers. It

may be dependent on a greater permeability of the hematoencephalic barrier or on greater biochemical similarity of bulbar interneurone synapses to ganglionic ones.

The pharmacological investigation of central cholinolytics has widened the scope of their therapeutical application. Soviet physicians are using them not only as tranquilizers in the treatment of mental and nervous troubles, but also in cases of certain neurogenic internal diseases as stenocardia, peripheral vascular spasm, bronchial asthma, etc. A comparison between the therapeutical effect obtained with cholinolytics of predominantly peripheral character, and those of preponderantly central action, when treating the same diseases, shows that the effect of the latter upon the central synapses is of importance in their curative action. It is quite possible that the curative effect observed in treating certain diseases as, for instance, arthrosis deformans, with these drugs stands in some relation with the activation of the adrenal cortex produced by central cholinolytics. Thus experimental data and clinical observations show that by acting with pharmacological substances upon cholinergic synapses one may exert a definite influence upon the CNS and upon its functions regulating the vital processes in the body.

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The main progress in the field of synaptic inhibition activity during the past few years has been brought about by the study of individual junctions. With intracellular electrodes a great variety of cases have now been analyzed. Therefore it seems timely to review the comparative physiology of inhibitory synapses in various cell systems and in different species. The lack excepting of certain features emerging from the synthesis of knowledge in an individual case. Very little work on synaptic mechanisms is strongly suggested in all instances of synaptic inhibition.

Electrical recording from postsynaptic cells has established one general phenomenon, namely that inhibitory neural summation tends to restore the membrane potential towards a particular level, usually at or near the resting potential, whenever deviations from this level occur. Thus if a cell is excited, i.e. is depolarized by

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CENTRAL INHIBITION

Presidente (Chairman): P. S. KUPALOV

BERITOFF, J. S.: *On the origin of the central inhibition.* (*Institute of Physiology of the Academy of Sciences of the Georgian SSR, Tbilisi, Georgia, URSS.*)

The origin of the central inhibition will be considered in regard to the cerebral cortex. Cortical inhibition may be well manifested in regard to the motor effects evoked from the cortex. While studying the influence of stimulation of different cortical regions on the motor effects induced by the stimulation of the motor cortex or sensible nerves in cats under the barbiturate anaesthesia, it was observed that the stimulation of motor, as well as of nonmotor cortex, which didn't give any motor reactions itself, inhibited the cortical motor effects. The threshold of the cortical inhibitory stimulation may be considerably lower than that usually necessary for producing motor effects by the stimulation of the motor cortex. This inhibition is general for the cortex because the depression of motor effects occurred on both sides of the body. Cortical inhibition began in the very first second and was observed under the lightest anaesthesia when stimulation of motor cortex or sensible nerve produced the general movement of animal (Beritoff and Gredevant, 1941). All this shows that the depression of cortical motor reactions took place as a result of inhibition of the cortex.

Central inhibition is well manifested in regard to spontaneous electrical activity too. For example, according to Roithbaks experiments (1951), stimulation of the suprasylvian gyrus at a frequency of 50 per second produces complete depression of the spontaneous electrical activity which lasts for some time after the cessation of the stimulation. The depression is manifested clearly at a near distance of about 1 mm and is not to be seen at all at a distance of 10 mm.

When an amplifier of great time constant is used, it can be seen quite clearly that the inhibition of the spontaneous ac-

tivity occurs during the negative DC potentials evoked by the tetanic stimulation of the cortex. This can be seen well not only with the high frequencies stimulation such as 50 and 100 per sec. but also with so low a frequency as 10 per second. From this it follows that the inhibition of the ~~spontaneous activity is not the result~~ as being a result of the increase of the stimulation frequencies, i.e. of the refractory state of the nerve elements producing the spontaneous electrical oscillations.

It is quite characteristic that stimulation of the cortex can depress also the initial positive potential of the primary responses. As the source of these electric waves is excitation of the pyramidal neurons of the deeper layers, it may be concluded that stimulation of the cortex during the superficial negative slow potentials inhibits also the pyramidal neurons (Beritoff and Roithbak, 1953).

According to the fact that the slow negative dendritic potentials, evoked by the stimulation of the cortical surface, coincide with the general cortical inhibition, as well as on the basis of other facts, we suppose that the weakening of the spontaneous electrical activity and of the primary responses are a result of the inhibitory effect of the slow dendritic surface potentials upon the corresponding nerve cells and their synapses. This inhibition of the cells and the synapses adjacent to them may become so great that excitation of these cells by way of these synapses may become impossible (Beritoff and Roithbak, 1955).

Twenty-five years ago we advanced the idea that at the basis of the inhibition of the nerve elements of the spinal cord and brain stem lies the anelectrotropic action of the slow potentials arising within the dendritic plexuses of the CNS and first of all in the brain stem reticular formation and substantia gelatinosa Rolandi in the spinal cord. It was thought that the electrotonic action took place by means of spreading of evoked currents through intercellular fluid to the nearest nerve elements or nerve

circuits (Beritoff, 1937, 1938). Somewhat later an analogous supposition was made in regard to cortical inhibition. It was ascribed to anelectrotonic action of the slow potentials of the dendritic plexuses in the cortex upon the nerve circuits and the axons of pyramidal cells (Beritoff, 1940). At that time we supposed that these slow potentials expressed the local nonspreading excitatory processes which arise in the dendrites when they are activated via synaptic endings of the afferent or internuncial neurons⁽¹⁾.

For the last 20 years our laboratory has been very active in studying the electrical manifestations of the activity of the central nervous system. The results we have obtained, we have attempted to confront with the latest concepts as to the brain structure.

On the basis of these recent data our theoretical concept about the anelectrotonic nature of the inhibition has constantly found, with the passage of time, more and more factual confirmation while being at the same time altered and refined.

First of all, it may be supposed that the slow positive potential, arising in the deep layers when the cortical surface is stimulated, produces a decreased excitability of the cellular elements of these layers as well as of the synapses lying upon the bodies of these cells.

One might think that this supposition was confirmed by experiments of Burns (1954). He applied D.C. to an area of only 0.77 mm². When the anode was applied to the cortex with a current strength of 100 μ A, the pyramidal neurons were excited. With the use of the cathode, the pyramidal neurons failed to become excited. When however the microelectrode was inserted into the cortex to a depth of 1.2 mm, i.e. into cortical layers V and VI, the pyramidal neurons would become excited with the application of the cathode.

(1) At that time the synaptic dendritic plexus producing the slow potentials was called by us a "neuropil", the term being used in the sense of the neurologist Judson Herrick and Ardens Kappers, as well as of the neurologist Zavarzin, who used this term for designating nerve plexuses of invertebrate animals even when these plexi did not have a synaptical character. As the term "neuropil" was commonly used to designate synaptical formations, such a use of the term led to misunderstandings; this circumstance caused us to refuse the use of "neuropil" when applied to a protoctyctial plexus.

and not the anode. When stimulating with strong induction shocks, the neurons became excited with a long afterdischarge. It is very characteristic that this subsequent period of excitation could be instantly terminated by applying the cathode to the cortical surface. Thus, it is clear that negative polarization of the apical dendrites results in inhibition of the pyramidal neuron activity. The impression is obtained that a catelectrotonus of the dendrite is combined with anelectrotonus of the cells.

It might be thought that we have here a phenomenon similar to the perielectrotonus of Wedensky (1920). When one area is polarized with a direct current, then, at a distance from the polarized area, say 20 mm, in some cases the electrical current may change its direction as for example, on the cathodal side at a distance of 20 mm the current has the same direction as the polarizing one, i.e., negative, while at a distance of 20-30 mm the direction of the current becomes positive. We have recorded this oscillographically precisely in those regions of the nerve where one can observe the so-called perielectrotonic alterations of the excitable state (Beritoff and Roitbak, 1956).

But these current alterations were observed by us on isolated myelinated nerves and, apparently, they are associated with structures characteristic for myelinated nerves and not for dendrites. But even in myelinated nerves these changes are far from being constant and the origin of the current reversals is not understood. For this reason, we cannot insist that the current reversals seen in the cortex with the slow potentials have the same physiological significance as when seen in the peripheral nerve.

This circumstance compelled us to search for another explanation of the inhibition without considering a reversal of the slow potential. It seemed to us that it was possible to associate the inhibition of the pyramidal cell with the electrical current which arises when the apical dendrites are excited locally. First of all it should be noted that the local dendritic processes do not reach the cell bodies. This can be deduced from the fact that when we stimulate the motor cortex by relatively weak shocks, the dendritic slow potentials arise within the stimulated zone without exciting the projection pyramidal cells, i.e., without causing any motor reactions. In order to

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excite them, it is necessary to markedly increase the strength of the stimulus or else to immerse the stimulating electrodes to the depth of the projection pyramidal cells (Adrian, 1936; Roitbak, 1953). From this we deduced that the apical dendrites do not conduct this excitation, i.e., the process of excitation of the dendrite does not spread to the cell body. The local process originating within the dendrites naturally does spread somewhat but the decrement is so great or else the current is so weak from the very beginning that the cell itself is not reached and so is not activated.

However, the current evoked by the local process may reach the cell body electrically. It might be asked why does it not produce local excitation here? This current does not excite the cell because of its relatively low amplitude or relatively low absolute strength. The slow changing current is below the threshold of local excitation of the cell.

Such a conclusion may seem improbable if we take into consideration the well-known fact that the dendrites of a single pyramidal neuron have thousands of synapses. Why then do not the local potentials reach the amplitude necessary to produce excitation of the cell?

First of all we must note that by the comparative histochemical investigations of dendrites and cell bodies was shown that the dendrites contain less quantity of protein and oxidizing ferment as succinodehydrogenase than the cell body and the synapses (Portugali, 1958). That means that the activity of the excitable system in dendrites must be somewhat lower than in the cells. As a result of this the intensity of the local dendritic process must be lower and the duration longer than in the cells. This in its turn must deteriorate the conditions for propagation of excitation along the dendrites. Besides that it may be thought that the peculiarities of the synaptic apparatus on dendrites play an essential role. As it is known upon the dendrites of the pyramidal neurons the synapses are not directly upon the surface of the dendrites but touch the lateral appendages, the so-called gemmules (Chang, 1952; Poliakov, 1953). These gemmules sit upon fine pedicles along the entire length of the dendrites with the exception of the initial divisions. It must follow then that the synaptic impulse, or more accurately speaking the rapidly flowing current of

synaptic excitation activates the head of the gemmules and that the process of excitation is then transmitted by way of the pedicle to the dendrite. But, because of the transmitting pedicle being only a half-micron in thickness, the excitatory process passing through it must become weakened. Accordingly within the dendrites under the gemmules there can arise only very weak local processes with low potentials.

Accordingly, the synaptic apparatus of the dendrites with gemmules has a completely special nature. Its biologic significance must consist, apparently, in weakening the local excitatory process.

It may be supposed that this dendritic electric current having reached the cell instead of exciting it, produces an inhibition. It is true that this electric current upon leaving the cell should excite it as is usual in regard to the action of electric current at the node where it enters into an excitable element, excitability falls, at the place of exit, excitability rises so that excitation may occur. Certainly, this physiological law is preserved intact in this instance. The case is that the entire surface of the pyramidal cell, as it was shown by de Castro (1951), is covered densely with glial layer. The same layer is between the synaptic bulb and cell surface too, but it is rather thin. The glial layer, from which the myelin membrane of nerve fibers develops, must conduct electrical current weakly. Therefore its electrical conductivity must be much greater under the synaptic bulbs than between them. Furthermore, one must bear in mind that electrical conductivity of those portions of the cell membrane adjacent to the synapses must be much greater than of the portions free of synapses because the cell permeability in the former is *much higher* due to the permanent impulse flux from the synapses. Therefore, electric current must come out the cell mainly through the synaptic areas. Having left the cell via these areas, the current must enter the synapses, and then come out the pre-synaptic fibers and spread to the active dendritic areas. Entering the synapses the electric current must affect them anelectrotonically and therefore reduce their excitability, even made them unexcitable. Thus the pyramidal cell must cease to respond to all impulses reaching it. Such an exclusion results in the disappearance of local excitatory processes within the cell as a consequence of which

- the excitability of the cell itself must become markedly lowered. In addition to all that has just been said, it should be remembered that the dendritic electric currents as coming out from the synaptic regions must compensate or neutralize the synaptic spike potentials. In this manner the cell is also protected from excitation across cellular synapses. According to this concept, the pyramidal cell and all the synapses upon it undergo a greater or lesser decrease of excitability each time the dendrites are excited.

Thus, we believe that the pyramidal cell is excited exclusively by way of the synapses adjacent to the cell body and to the apical portions of the dendrites under the influence of synaptic spike potentials; the synapses adjacent to the dendrites produce the slow dendritic currents which inhibit the pyramidal cell.

As it comes out from the whole hypothesis, the dendritic inhibition of cell may occur partially due to the depression of a part of synapses located rather near to active dendrite. Thus this pyramidal cell may be excited via other undepressed synapses located far enough from the active dendrites.

But all the pyramidal cells possess, in addition to the apical dendrites, numerous basal dendrites. These last travel only short distances and do not leave the limits of the layer in which the cell lies. These dendrites are also covered by lateral appendages-gemmules. It follows that the cell may be inhibited also by activation of the basal dendrites. The histological studies of Poliakov (1953) have demonstrated that the basal dendrites are crossed by the collateral axons of the neighboring pyramidal neurons. This permits us to assume that excitation of any pyramidal neuron, by way of its collaterals an activation of the basal dendrites of the neighboring neurons thus inhibiting them. It must be by these means that there is accomplished an inhibition of the neurons around the focus first excited. Apparently, the neighboring neurons become unresponsive in relation to those impulses which reach their bodies from the excited neuron complex. This must explain why the impulses of an even convulsive excitation produced by powerful electrical cortical stimulation or after local strychnine poisoning fail to spread throughout the entire cortex. Usually they are limited to the stimulated or poisoned

region and to symmetrical areas on the opposite hemisphere as well. Around the excited focus, spontaneous electrical activity is, to the contrary, depressed which seems to be evidence that, in the pyramidal neurons around the excited focus, the excitability is decreased, i.e., they are inhibited.

But after repeated application of strychnine the excitability of the entire cortex is increased as a result of its spreading. In some cases the convulsive discharges are observed in other cortical regions as well. But these discharges occur independently with the different rhythm. The convulsive discharges do not influence on each other (Beritoff and Gedevanishvili, 1945).

The question about the origin of cortical inhibition concerns to all pyramidal neurons, to projective cells, their axons descending to subcortex, to associative cells connecting the different cortical areas by means of their axons passing through the white matter of subcortex, and to inter-nuncial pyramidal neurons connecting the different regions of the cortex in vertical and horizontal directions without leaving it. But besides the pyramidal neurons there are the stellate (star like) cells with short axons in the cortex, forming the great majority of III-IV cortical layers of the central region of perceiving areas, s.c. analysers in the highest mammals.

These stellate neurons with short axons in most cases possess few dendrites of small length. Besides that the dendrites of stellate neurons have few gemmules or have them not at all. But they, in contrary to dendrites of pyramidal neurons, are provided with small thickenings along the entire length of dendrites (Chang, 1952; Poliakov, 1953). There are such stellate neurons in layers IV and III of the cerebral cortex of the cat, especially in area 17, that compose the majority of the neurons present. We must assume that the same situations exist in the central territories of other analyzers. It is in these central territories that the afferent thalamic fibers terminate and, therefore, they must be associated synaptically mainly with the stellate neurons. As the dendrites of these neurons do not have lateral appendages, the synapses must lie directly upon their surfaces or upon the body of the cell. Therefore, under the influence of synaptic impulses there must arise quite strong local processes which can spread for greater distances than is the case with the dendrites.

of the pyramidal neurons. The presence of beading upon the dendrites must in its turn also favor the intensity and spread of the local processes. Following this reasoning it might be supposed that the dendrites of the stellate neurons conduct the process of local excitation up to the cell body and that they participate in the initiation here of a propagated excitation. Thus in the stellate neurons with the short axons the synapses present upon the cell bodies as well as upon the dendrites apparently, subserve the function of excitation.

Then, how are these stellate neurons inhibited? There are known numerous facts which prove that under given conditions excitability or the reactivity of the stellate neurons diminishes, they become refractory and their activities become inhibited. Thus (for example, we have already described how the cortical stimulation not only inhibits spontaneous electrical activity but also inhibits the primary electrical effects which arise in the central territory of the auditory analyzer after stimulation of the auditory receptor. How would it be possible to suppress the primary effects if not by way of primary inhibition of the stellate neurons? This depression of the primary responses might be a secondary consequence of the inhibition of the activity of those interneuronal and association neurons which participate in the production of the primary responses for, with the disappearance of impulses leaving them, the level of excitability of the stellate cells also falls.

It must be supposed that the stellate neurons receive impulses from the interneuronal and association neurons of cortex as well as from the nonspecific thalamic fibres and by this secure at all times a high grade of excitability and a great receptivity to peripheral impulses coming from the different specific thalamic pathways. For this reason the exclusion of the inter-central impulses must lead to a depression of the sensitivity of the stellate neurons to external stimuli.

There are no known physiological facts proving that the stellate cells perceiving specific thalamic impulses undergo primary inhibition. It is true that we are observing constantly both inhibition and excitation of reflex cortical activities. But usually in human experiments it is easy to show that the inhibition of an external reaction is not conditioned by the inhibition of the stellate

cells. Thus, for example, when conditioned reflexes are being differentiated or extinguished, the given stimulus continues to be perceived in spite of the disappearance of the reflex itself. Apparently, within the cortex the interneuronal and association neurons going to the projection pyramidal neurons or else, these latter themselves are inhibited even while the stellate cells continue to perceive the external stimulus.

Even in animal experiments it can be shown that when conditioned reflexes are differentiated or extinguished we are not dealing with inhibition of the cortical receptor neurons. It is known that the differentiated stimuli, as well as conditioned stimuli of an extinguished reflex, do not produce ~~any external reaction but~~ depress other conditioned reflexes. Obviously, this could not occur without activation of the cortical receptive apparatus, without excitation of the stellate cells of the corresponding analyzer.

All these facts are clear proof that the stellate cells are not inhibited directly by the influence of peripheral impulses. It is quite permissible to regard them as being inhibited as a result of inter-central impulses coming by way of the specific thalamic fibres or the association and interneuronal neurons. After all, it is a well-known fact that when the human or animal cortex is pre-occupied with some pursuit important to life, it will not react markedly to numerous external stimuli. The person may not even feel them. However, this fact does not at all prove that the receptor stellate cells of the entire cortex, with the exception of those performing the given task important to life, are of necessity inhibited. As has been shown above, general cortical inhibition is mediated through the activation of the apical dendrites of the first cortical layer. These ~~are distributed among~~ different pyramidal neurons. The ~~apical~~ neurons do not have dendrites in this surface layer and therefore cannot be inhibited in this manner. The absence of a corresponding reaction to an external stimulus may occur without inhibition of the stellate neurons due to the inhibition of all those association and interneuronal neurons by means of which the stellate neurons accomplish the external reaction. The absence of a subjective sensation is not evidence that the receptor stellate cells are inhibited. This may be the consequence of their lowered sensitivity because of the in-

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hibition of the nonspecific neurons of the activating system as well as of the association and intermuncial neurons which serve to facilitation and integration of the activity of the stellate neurons.

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L'inhibition nerveuse centrale, de même que l'excitation, s'observe et s'analyse à divers étages de complexité. Elle se manifeste extérieurement dans les modalités du comportement animal, et à cet étage les observations sur le rôle déterminant de l'inhibition dans les réflexes conditionnés sont, depuis Pavlov, particulièrement riches en enseignements. Les réflexes expérimentaux de la neurophysiologie classique fournissent de leur côté un ensemble cohérent de faits que l'on doit principalement — hommage étant d'abord rendu à Satchenov⁴⁴ pour avoir relaté, en 1863, le premier exemple d'inhibition centrale expérimentale — aux travaux de Sherrington et de ses élèves et continuateurs, parmi lesquels il convient, en cette

matière, de citer notamment Denny-Brown, Liddell, Eccles, Bremer, Fulton. À ce type de recherches appartiennent aussi les travaux de l'école russe, avec Beritov (1924)⁴⁵, Samoilov et Kissilev (1927)⁷². Aujourd'hui, avec le progrès des techniques électro-microphysiologiques, c'est dans la profondeur des centres mêmes, et jusqu'à l'échelle du neurone individuel et de ses infra-structures, que l'on sait aller chercher les témoins de l'inhibition nerveuse centrale.

C'est évidemment à ce dernier stade de l'analyse qu'il faut finalement se placer pour atteindre les bases du processus. Sur sa nature, les anciens expérimentateurs, à partir des données indirectes dont ils disposaient, avaient déjà longuement et diversement spéculé. Leurs inférences n'étaient pas toutes mauvaises. Ainsi, la notion d'une symétrie possible entre les processus intimes de l'excitation et de l'inhibition fut soutenue avec vigueur aussi bien par Sherrington (C. I. S. versus C. E. S.) que par Pavlov ("... le processus inhibiteur, antipode du précédent" c'est-à-dire de l'excitation)⁶⁸, et nous savons aujourd'hui qu'elle repose sur une réalité biophysique. Une autre question est celle de l'unicité ou au contraire de la multiplicité, des processus inhibiteurs normaux (les formes purement artificielles de dépression étant exclues de notre intérêt). Elle semble surtout affaire de définition et il est tentant de restreindre, comme le fait Eccles (1957)²⁸, le concept de l'inhibition centrale aux phénomènes dépressifs qui n'impliquent pas une excitation préalable de la structure explorée, c'est-à-dire à ce qu'on nomme *inhibition directe*: car c'est cette inhibition directe dont l'existence fut expérimentalement démontrée à la même date (1941) par Renshaw⁷¹ et par Lloyd⁵⁰, qui semble avoir largement la prépondérance, sinon l'exclusivité. Nous admettrons ici cependant une définition plus large du concept, lequel, selon l'habitude courante, doit pouvoir englober sous l'expression d'*inhibition indirecte*, les formes d'action dépressive consécutives à une excitation de la structure étudiée, lorsque des influx autres que ceux participant à l'activité-test sont venus y converger, à condition que ces influx ne soient pas eux-mêmes capables de déclencher une réponse identique à la réponse-test (ce qui revient à éliminer les cas d'occlusion pure par influx efficaces pour produire la réponse-test).

Nous terminerons par quelques considérations générales sur l'incorporation de